## REMARKS

### STATUS OF THE CLAIMS

Claims 1, 2, 4-10, 12-15, 19, and 20 were pending in this application. Claims 1 and 20 have been amended. Claim 21 has been added, reinstating previously cancelled claim 3. New claim 22 has been added. Following entry of the amendments, claims 1, 2, 4-10, 12-15, and 19-22 will be pending and at issue.

### SUPPORT FOR AMENDMENTS TO THE CLAIMS

Claim 1 has been amended in response to the Examiner's suggestion to overcome an objection to the claims.

Claim 20 has been amended to include the term "SEQ ID NO:3" to more clearly define Applicant's invention. Support for the term "SEQ ID NO:3" can be found throughout the specification as filed, e.g., page 84, example 17.

New claim 21 reinstates original claim 3, and finds support in the claims as filed.

New, dependent claim 22 has been added to claim one species of the Markush group of claim 21 (originally claim 3 as filed) and finds support in the claims as filed..

The amendments to the claims therefore add no new matter.

### REINSTATEMENT OF CLAIM 3, NOW CLAIM 21

In the Preliminary Amendment dated August 27, 2002, Applicant cancelled claim 3 without prejudice in response to a telephone interview with the Examiner on August 27, 2002. Applicant has reinstated claim 3 herein as new claim 21.

Applicant notes that in a number of other cases, the USPTO has issued restriction requirements for claims that are similar to new claim 21 of this application. In the event that the Examiner decides to issue a restriction requirement in this case, Applicant will elect the species of SEQ ID NO:22. In addition, Applicant will identify Claims 1 and 2 as linking or genus claims because they link the inventions of SEQ ID NOS: 13, 14, 16, 17, 18, 19, 22, 23, 25, 26, 27, 29, 30, 31, 33, 35, 40, 41, 43, 45, 46, 47, 48, 49, 51, 53, 54, 55, 56, 57, 59, 60, 61, 64, 65, 66, 67, 68, 69, 70, 71, 72, 74, 76, 78, 81, 84, 87 and 88. Applicant will do this with the understanding that

the Examiner will examine Claims 1, 2, and 21 with elected SEQ ID NO:22. If claims 1 and 2 are allowable, all of the inventions of SEQ ID NOS: 13, 14, 16, 17, 18, 19, 22, 23, 25, 26, 27, 29, 30, 31, 33, 35, 40, 41, 43, 45, 46, 47, 48, 49, 51, 53, 54, 55, 56, 57, 59, 60, 61, 64, 65, 66, 67, 68, 69, 70, 71, 72, 74, 76, 78, 81, 84, 87 or 88 will then be subject to examination.

Applicant respectfully points out that any restriction requirement of claim 21 should be a ***species election***, so as to not restrict within a single claim. Although restriction within a single claim is legally improper, the Patent Office is not required, at least initially, to specifically examine every species encompassed by a generic claim, e.g., every sequence covered by claim 21. The procedure for handling applications that include generic claims is set forth in 37 CFR § 1.146. This rule provides that "[i]n the first action on an application containing a generic claim to a generic invention (genus) and claims to more than one patentably distinct species embraced thereby, the examiner may require the applicant in the reply to that action to elect a species of his or her invention to which his or her claim will be restricted ***if no claim to the genus is found to be allowable***." As stated in MPEP § 809.02(a), "[u]pon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141."

Thus, where generic claims are present, an applicant may be required to elect a species for initial examination, but the generic claims are still subject to examination to determine whether such generic claims are allowable.

MPEP § 806.04(b) states that species may be related inventions. Specifically this section of the MPEP directs that:

> [w]here inventions as disclosed and claimed are both (A) species under a claimed genus and (B) related, then the question of restriction ***must*** be determined by both the practice applicable to election of species and the practice applicable to other types of restriction such as those covered in MPEP § 806.05- § 806.05(i). If restriction is improper under either practice, it should not be required.

The species set forth in claim 21 (particular oligonucleotide sequences) fall within the genus of claim 1 (compounds targeted to a nucleic acid encoding Trip6) and the subgenus of claim 2 (antisense oligonucleotide compounds targeted to a nucleic acid encoding Trip6). The species are also related: each species is a compound that both hybridizes to and inhibits the expression of Trip6 and may even overlap. Therefore, as described above, "the question of restriction must be determined by both the practice applicable to election of species and the practice applicable to other types of restriction such as those covered in MPEP § 806.05-§ 806.05(i)."

Election of species practice strikes an appropriate balance between the interests of the Patent Office in promoting administrative efficiency and avoiding unduly burdensome examination, and the clear constitutional and statutory rights of an inventor to claim an invention as it is contemplated, provided the dictates of 35 U.S.C. § 112 are satisfied. *See, e.g.*, MPEP at 803.02; *In re Wolfrum* 179 USPQ 620 (CCPA, 1973); *In re Kuehl* 177 U.S.P.Q. 250 (CCPA, 1973). Unlike a restriction requirement, an election of species requirement does not preclude an applicant from pursuing the original form of a claim in subsequent prosecution, nor does it force an applicant to file multiple divisional applications that will not capture the full scope of the invention.

**OBJECTIONS TO CLAIMS**

**Claims 1, 2, 4-10, 12-15, 19, and 20** were objected to for use of the article "a" in lines 2-3 of claim 1 ("a 5'-untranslated region, a start codon region, a coding region, or a 3'-untranslated region of a nucleic acid molecule") as allegedly improper "since all the limitations are drawn to the nucleic acid." Without agreeing with the Examiner's position but to expedite prosecution, Applicant has amended Claim 1 as suggested by the Examiner, by replacement of the article "a" with the article "the."

**REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH**

**Claims 1, 2, 4-10, 12-15, 19, and 20** were rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite because they recite or depend from the term "compound." The

Examiner states that the term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. The Examiner suggests replacement with the language "antisense nucleic acid."

Applicant respectfully disagrees. One of skill in the art would be reasonable apprised of the scope of the invention by reading the specification. The term compound is described at length in the specification at, e.g., page 11, lines 18-31:

> While antisense oligonucleotides are a preferred form of antisense compound, the present invention comprehends other oligomeric antisense *compounds*, including but not limited to oligonucleotide mimetics such as are described below. The antisense *compounds* in accordance with this invention preferably comprise from about 8 to about 50 nucleobases (i.e. from about 8 to about 50 linked nucleosides). Particularly preferred antisense compounds are antisense oligonucleotides, even more preferably those comprising from about 12 to about 30 nucleobases. Antisense *compounds* include ribozymes, external guide sequence (EGS) oligonucleotides (oligozymes), and other short catalytic RNAs or catalytic oligonucleotides that hybridize to the target nucleic acid and modulate its expression.

Other variations of preferred compounds are further described on pages 11 through 21 and include, e.g., oligonucleotides containing modified backbones, oligonucleotides with one or more substituted sugar moieties, LNA's, oligonucleotides with nucleobase modifications or substitutions, conjugated oligonucleotides, chimeric oligonucleotides, and the like.

Therefore, claims 1, 2, 4-10, 12-15, 19, and 20 are not indefinite because one of ordinary skill in the art would be reasonably appraised of the scope of the invention. Applicant respectfully requests withdrawal of this rejection.

**Claim 19** was rejected as allegedly indefinite because of the term "differentially inhibits." The Examiner states that the term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of metes and bounds of the term. Claim 19 was also rejected as allegedly

indefinite because it is unclear to the Examiner what is meant by "relative to the remaining variants of thyroid hormone receptor interactor 6."

Applicant respectfully disagrees. One of skill in the art would understand that Claim 19 covers a compound that inhibits to a greater degree, e.g., differentially inhibits, expression of one or more variants of thyroid hormone receptor interactor 6 as compared to the inhibition of expression of other variants of thyroid hormone receptor interactor 6 by the same compound. For support, Applicant directs the Examiner's attention to Example 17 on page 84 of the specification, where 5 embodiments of the compounds claimed by Claim 19 are disclosed. Hybridization and the effects on expression were examined using 5 antisense oligonucleotides and two target nucleic acids; both targets were variants of thyroid hormone receptor interactor 6: TRIP6-I (SEQ ID NO:3) and TRIP6-II (SEQ ID NO:11). TRIP6-II is an exon 1- exon 3 splice variant of thyroid hormone receptor interactor 6. Example 17 discloses that 4 compounds, e.g., SEQ ID NOS:15-18, specifically hybridize with and differentially inhibit, e.g., inhibit to a greater degree, the expression of TRIP6-I relative to the expression of TRIP6-II. One compound, e.g., SEQ ID NO:89, specifically hybridizes with and differentially inhibits, e.g., inhibits to a greater degree, the expression of TRIP6-II relative to the expression of TRIP6-I.

Therefore, Applicant believes that Claim 19 is not indefinite, and requests withdrawal of this rejection.

**Claim 20** stands rejected as allegedly indefinite because it recites the term "TRIP6-I." The Examiner states that the term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of metes and bounds of the term TRIP6-I.

Applicant respectfully points out the term is defined in the specification on page 84, where TRIP6-I is defined as thyroid hormone receptor interactor 6 (SEQ ID NO:3). However, without agreeing with the Examiner's argument, but to expedite prosecution, Applicant has amended Claim 20 to include the language "SEQ ID NO:3." Withdrawal of this rejection is requested.

**REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH**

Applicant acknowledges withdrawal of the Examiner's earlier rejection under 35 U.S.C. § 112, first paragraph.

**REJECTIONS UNDER 35 U.S.C. § 102**

Applicant acknowledges withdrawal of the Examiner's earlier rejection under 35 U.S.C. § 102(b).

**REJECTIONS UNDER 35 U.S.C. § 103**

**Claims 1, 2, 4-10, and 12-14** are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Schneider (Forschungszentrum Karlsruhe (2001) FZKA 6587:1-139) in further view of Baracchini et al (US Patent No. 5801154) and Fritz et al (Fritz et al (1997) Journal of Colloid and Interface Science 195:272-288). Applicant traverses this ground of rejection.

The claimed invention is a compound targeted to a 5'-untranslated region, a start codon region, a coding region, or a 3'-untranslated region of nucleic acid encoding Trip6 (thyroid hormone receptor interactor 6, SEQ ID NO:3) wherein said compound hybridizes to and inhibits expression of the nucleic acid. The invention also includes dependent claims where the compound is an antisense oligonucleotide that has various recited modifications and where the antisense compound is included in various carriers.

The Examiner has presented the combination of Schneider (a German language dissertation allegedly demonstrating reduction of Trip6 protein by antisense techniques) with art that teaches antisense inhibitory molecules of a specific, non-Trip6 target, Baracchini et al (teaching antisense modulation of multidrug resistance-associated protein, or MRP), together with Fritz et al (teaching cationic polystyrene nanoparticles as carrier systems for antisense compounds in general). The Examiner has failed to make a prima facie case of obviousness for the following reasons:

I. Schneider is not clearly available as prior art;

II. The combination of art cited by the Examiner is based on improper hindsight and does not provide a teaching or suggestion to combine the teachings;

III. One of skill in the art would have had no expectation of success when combining the elements taught by the cited combination of art.

I. The availability of Schneider as prior art is unclear.

Applicant thanks the Examiner for the phone interview of September 11, 2003 regarding the English translation of the Schneider dissertation and the date Schneider was publicly available. Applicant acknowledges receipt of the pages translated from German into English: 2 cover pages, 38 (partial), 86 (partial), 87, 88, and 89 (partial).

The Examiner has cited Schneider in both this Office Action and the Office Action dated September 11, 2002, paper number 5 (09/11/02 Office Action). Applicant respectfully points out that the date this dissertation was publicly available cannot be determined using either the material provided by the Examiner or Internet and library searching on the part of Applicant. Applicant respectfully requests that a publication date be provided.

The paper copy provided by the Examiner has a date of 2001 on it, but whether this refers to the publication date or the date the dissertation was completed and/or approved is unknown. In addition, since the instant application was filed on November 8, 2001, a more precise date than "2001" would be required to determine whether or not Schneider is available as prior art. Applicant notes that, if a prior art disclosure has been retrieved from the Internet and does not include a publication date or retrieval date, it cannot be relied upon as prior art under 35 USC 102 (a) or (b). See MPEP 2128.

During the interview of 9/11/03, The Examiner indicated that the dissertation was publicly available on the date of the oral presentation, or May 7, 2000. Applicant respectfully points out that the date a dissertation is publicly available is, e.g., the date it is placed in a university library and is sufficiently accessible to the public. See MPEP 2128.01.

II. The combination of Schneider with Baracchini et al and Fritz et al provides no motivation to combine and, instead, is based on improper hindsight.

Assuming that Schneider is available as prior art, and Applicant does not concede that it is, the Examiner's rejection is improper because there is no motivation (outside Applicant's own disclosure) to modify or combine the teachings of Schneider with Baracchini et al and Fritz et al to obtain the specific compounds of the claims, e.g., compounds that hybridize to the a 5'-untranslated region, a start codon region, a coding region, or a 3'-untranslated region of nucleic acid encoding Trip6. Instead, the combination is impermissible hindsight based on Applicant's own disclosure.

To render a claim unpatentable under 35 U.S.C. § 103, there must be some suggestion or motivation, either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. The teaching or suggestion to make the claimed combination must be found in the prior art, not in applicant's disclosure. *In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP §§ 2143, 2143.01.

Schneider teaches the use of "antisense techniques" to inhibit Trip6. In the 09/11/02 Office Action, the Examiner stated that Schneider further disclosed a reverse PCR oligonucleotide primer of 27 nucleobases in length on page 41. Schneider does not teach antisense oligonucleotides to the specific regions recited by the claims, e.g., a 5'-untranslated region, a start codon region, a coding region, or a 3'-untranslated region of a Trip6 nucleic acid.

Fritz et al clearly dos not remedy this deficiency, teaching nothing about the specific regions recited by the claims.

The Examiner cites Baracchini et al as providing the teaching for the specific regions cited in Applicant's claims. Applicant submits that the teachings of Baracchini et al identified by the Examiner would be interpreted by one of ordinary skill in the art as pertaining specifically to the MRP gene target. There is nothing in the Baracchini et al to suggest that an ordinarily skilled artisan would read the disclosures as a generic teaching to design antisense oligonucleotides

targeted to any and all disease-associated gene targets. That is, there is nothing in Barrachini et al to suggest or motivate on e of skill in the art to combine Schneider with Barrachini et al. Rather, Baracchini et al teaches antisense oligonucleotides to a specific target, e.g., multidrug resistance-associated protein (MRP).

Applicant respectfully points out that the Examiner has misstated the passages from Baracchini et al. For example, on page 4 of the Office Action, the Examiner cites Baracchini et al as follows:

> Baracchini et al teach antisense oligonucleotides that can specifically hybridize with a 5'-untranslated region, a start codon region, a coding region, or a 3'-untranslated region of a target gene (see column 9, lines 6-67 and column 10, lines 1-25 and table 1). Thus, one of ordinary skill in the art would have been motivated and expected success to make an antisense compound targeting specific regions such as the 5'-untranslated region, the start codon region, the coding region, or the 3'-untranslated region nucleic acid molecule encoding thyroid hormone receptor interactor 6 because it is well known in the art to target different sites/regions within a gene for the oligonucleotide interaction to occur such that a desired effect (e.g., detection or modulation of expression of protein) will result.

There is nothing in the reference to suggest that an ordinarily skilled artisan would read its disclosure as a generic teaching to design antisense oligonucleotides targeted to, e.g., a 5'UTR, coding region or a 3'UTR of any and all disease-associated gene targets. Applicant submits that the teachings of Baracchini et al identified in support of the Examiner's combination instead would be interpreted by one of ordinary skill in the art as pertaining specifically to the MRP gene target. The Baracchini et al section on targeting supports this conclusion:

> In the present invention, the target is a nucleic acid encoding multidrug resistance-associated protein. The targeting process also includes determination of a site or sites within this gene for the oligonucleotide interaction to occur such that the desired effect, e.g., detection or modulation of expression of the protein, will result.

Baracchini, col. 9, lines 14-19, emphasis supplied.

> In the context of the invention, "start codon" and "translation initiation codon" refer to the codon or codons that are used in vivo to initiate translation of an mRNA molecule transcribed from a gene encoding MRP, regardless of the sequence(s) of such codons.

*Id.* at col. 9, lines 39-43, emphasis supplied.

> Other target regions include the 5' untranslated region (5'UTR), known in the art to refer to the portion of an mRNA in the 5' direction from the translation initiation codon, and thus including nucleotides between the 5' cap site and the translation initiation codon of an mRNA or corresponding nucleotides on the gene and the 3' untranslated region (3'UTR), known in the art to refer to the portion of an mRNA in the 3' direction from the translation termination codon, and thus including nucleotides between the translation termination codon and 3' end of an mRNA or corresponding nucleotides on the gene).

*Id.* at col. 9, line 60 through col. 10, line 3, emphasis supplied.

> In preferred embodiments of the present invention, the oligonucleotides are specifically hybridizable with a transcription initiation site, a translation initiation site, coding sequences and sequences in the 5'- and 3'-untranslated regions of mRNA encoding MRP.

*Id.* at col. 10, lines 20-25.

Similarly, each of the antisense oligonucleotides listed in Table 1 is directed to regions of the MRP gene, as evidenced by the table title. Thus, the references in Baracchini et al to 5'-UTR, coding region and 3'-UTR targets all are tied to the MRP gene, the expression of which Baracchini's invention seeks to inhibit. There is nothing to suggest that one of ordinary skill reading Baracchini et al would interpret its teachings in the expansive manner suggested by the Examiner and so combine them with those of Schneider.

Accordingly, the combination of Schneider, Baracchini et al, and Fritz et al all provides no motivation to combine the elements recited by the claims. Instead, the combination is motivated by Applicant's own disclosure and so cannot be relied upon to make out a prima facie case of obviousness. Accordingly, the claims are patentable over the cited art.

III. Inhibitory antisense oligonucleotide design at the time of the invention was not sufficiently predictable from gene to gene to provide a generic reasonable expectation of success.

Even if Applicant were to assume *arguendo* that Schneider was available as prior art and that the Examiner properly had identified a motivation to combine the cited references, the 35 U.S.C. § 103 rejection still would be improper. Modifying or combining art to make out a prima facie case of obviousness also requires that the prior art provide an ordinarily skilled artisan working at the time of the invention with a reasonable expectation of success in making the claimed invention. MPEP § 2143.02.

Applicant submits that the cited references fail to provide a reasonable expectation of success because the cited references, alone or in combination, fail to provide direction as to which of many possible choices of Trip6 antisense molecules was likely to be successful. As such, the cited combination at best makes the claimed invention "obvious to try." It does not render it obvious. *See In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

Given the completely unrelated sequences of nucleic acids encoding Trip6 on the one hand and those encoding MRP on the other, there is nothing in the approaches to designing antisense oligonucleotides used by Baracchini et al nor in the sequences of the specific antisense molecules found by Baracchini et al that could provide direction as to the successful selection of antisense molecules that would specifically hybridize with and inhibit expression of a Trip6 nucleic acid molecule. Fritz et al does not remedy this deficiency. Thus, the cited combination fails to make out a prima facie case of obviousness.

In conclusion, a prima facie case of obviousness is not made. Withdrawal of this ground of rejection of claims 1, 2, 4-10, and 12-14 is respectfully requested.

## CONCLUSION

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions

concerning this Response, the Examiner is invited to telephone Applicant's representative at (415) 875-2316.

Respectfully submitted,
BENNETT ET AL

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